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COVID-19 Vaccines Are Entering Uncharted Immune Territory

Some people's bodies aren't set up for vaccines.

KATHERINE J. WU APRIL 15, 2021

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In early March 2020, Rick Phillips, 63, and his wife, Sheryl Phillips, quietly cloistered themselves in their Indianapolis home. They swore off markets, movie theaters, the gym, and, hardest of all, visits with their three young grandchildren. This April, three weeks after receiving her second shot of Pfizer's vaccine, Sheryl broke her social fast and walked into a grocery store for the first time since last spring. Rick has yet to join her. He received his shots on the same days his wife received hers. By official standards, he, too, can count himself as fully vaccinated. But he feels that he cannot *act* as though he is. "I personally remain scared to death," he told me.

Rick has rheumatoid arthritis, which once rendered him "barely able to walk across the room," he said. He now treats the condition with an intensely immunosuppressive drug that strips his body of the ability to churn out disease-fighting antibodies. Rick credits the treatment with changing his life. But it might also keep him from developing lasting defenses against COVID-19.

Vaccines have promised, to the rest of the world, a return to a semblance of normal life; the ones currently cleared for use against the coronavirus are, by all accounts, extraordinary. But they were not designed for, or tested extensively on, immunocompromised or immunosuppressed individuals, whose immune systems have been subdued by underlying conditions, environmental exposures, drugs, or

viruses such as HIV. With their defenses down, many of these people can't yet count on what the rest of us can: that the new shots will protect them from the coronavirus.

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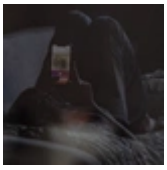

The Danger of a 'Dudes Only' Vaccine

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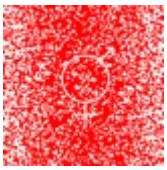

The benefits of vaccination still far outweigh the risks: Experts told me they had no safety concerns about vaccinating people with weakened immune systems, who are often at higher risk of getting severe COVID-19. And in signing up for their shots, Rick and others like him can also help fill the data void that the clinical trials left, and potentially advance our understanding of how vaccines guard against the virus. Certain immunosuppressive drugs will undermine the vaccines in different ways; by pinpointing where, how, and in whom the shots most often falter, scientists might be able to discover which parts of the immune system are most essential for immunity against the coronavirus. "We still don't understand why only certain people get so sick and die [from COVID-19]," Meena Bewtra, a clinical epidemiologist at the University of Pennsylvania who treats patients with inflammatory bowel disease, told me.

But inoculating the immunocompromised remains, in some ways, fraught. As the vaccine rollout continues, many people with weakened immune systems are unsure of how to navigate their post-vaccination existence. The milestone they must wait

for isn't their *own* vaccination, but *everyone else's*—when society reaches an immunological tipping point that will shield the still-vulnerable from the disease.

There is no single way to build a well-functioning immune system. But there are countless ways to derail one.

A typical immune system, if such a thing exists, relies heavily on precision and coordination. The body must first accurately distinguish an assailant from its own healthy tissue, then launch a series of well-timed attacks without marshaling extraneous fighters to the fore. The what, when, and where of these immunological assaults are all crucial to the body's ability to waylay disease; any perturbation threatens to set the whole system askew.

[Read: The body is far from helpless against coronavirus variants]

Some people are born with genetic mutations that hamstring immune cells' abilities to recognize and thwart infections; others struggle to mount strong responses because of environmental causes, such as poor nutrition, cancers, or chemotherapies and pathogens that attack some of the body's most potent defenders. Immunosuppression can also be an intentional, lifesaving tactic. Drugs that deliberately muzzle immune cells can help people with autoimmune conditions, such as rheumatoid arthritis, lupus, multiple sclerosis, and inflammatory bowel disease; organ-transplant recipients must take them, typically for the rest of their lives, to boost tolerance for unfamiliar tissue.

Overlaying vaccines onto this inherent diversity becomes a complex tangle. Vaccines are intel-packed training regimens designed for well-functioning immune cells—rookie soldiers who can sponge up info, strategize with their peers, and prepare for an upcoming encounter with a dangerous microbe. But the protection calculus changes when the contents of the shots are met by fighters who have been restrained.

Some medications are expected to present a slight setback, but aren't necessarily disastrous for COVID-19 immunization, because they suppress just a sliver of the immune system's typical operations. One example is ustekinumab (Stelara), a common treatment for Crohn's disease, which zaps the signals that immune cells

send one another—an intervention akin to temporarily putting a military's radio system on the fritz. Many of these treatments can continue on schedule during vaccination, under the advisement of a physician.

Other drugs, however, are far blunter tools, clobbering large swaths of the immune system. Among them is Rick Phillips' drug, rituximab (Rituxin), which is used to treat rheumatoid arthritis, multiple sclerosis, lupus, and white-blood-cell cancers such as leukemia and lymphoma. It destroys entire populations of B cells—on par with blitzing a fleet of naval forces. B cells are antibody factories, and without them the immune system has more difficulty committing new viruses to memory. "We've pharmacologically made a hole in the immune system," Erin Longbrake, a neurologist at Yale New Haven Hospital who is studying COVID-19 vaccine responses in multiple-sclerosis patients, told me. After a rituximab infusion, B cells can take six months or more to bounce back.

The lasting impacts of B-cell-depleting therapies have prompted many physicians to recommend that such drugs be administered with careful timing around a COVID-19 shot. "It's the medication I worry about the most," Anna Helena Jonsson, a rheumatologist at Brigham and Women's Hospital, in Boston, told me. Rick Phillips was three months out from his most recent infusion of rituximab when he received his first dose of Pfizer's vaccine, in February. He pushed back his next infusion until mid-April—a month later than usual—in hopes of giving his COVID-19 shots' protective powers time to take hold.

[Read: Immunology is where intuition goes to die]

People who have an autoimmune disease that's poorly controlled, though, could risk a symptom flare by delaying their medications; others who have received organ transplants, or who are at the beginning or middle of a chemotherapy course, can't simply flip their medications off. Some people will need to prioritize their existing treatment, "then just get the vaccine when you can," Chaitra Ujjani, an oncologist at the Seattle Cancer Care Alliance who is studying COVID-19 vaccine responses in people with blood cancers, told me.

People living with HIV are facing a different type of immune deficit. The virus annihilates immune cells called helper T cells, which coax young B cells into churning out antibodies and spur other T cells, called killers, to assassinate infected cells. Without helper T cells, the body's coordinated defenses against disease very

often crumble. “We know from other vaccines that people with very low [helper T-cell] counts do not mount a good response,” Boghuma Kabisen Titanji, an infectious-disease physician who works with HIV patients at Emory University, told me. Potent antiretroviral therapies can buoy helper T-cell counts, but they don’t work for everyone. Titanji’s strategy with her patients has been to manage expectations about vaccination: “You will get some protection, but I can’t tell you for certain you’ll have the same degree of protection as others.”

“We’re still telling them to use full precautions and social distance” after vaccination, Ujjani told me of her own patients. Some people might benefit from the most conservative approach of all, she said: “It’s almost as if the vaccines didn’t exist.”

Laboratory immunology is often a game of subtractions and additions. Scientists will snuff out certain genes, or monitor the health of animals with faulty immune cells, and see how they react to a bevy of infections. Translating those results to humans is inevitably messy; researchers can’t tinker with the health of people in the same invasive ways. But vaccinating real, diverse patient populations could offer a similar set of immunological hints. Multiple sclerosis and other autoimmune diseases, for example, can be treated with a multitude of drugs, each targeting a slightly different branch of the immune system. John Wherry, an immunologist at the University of Pennsylvania, told me that he and his colleagues hope to suss out which of these medications most often punches holes in vaccine-induced protection: If one group of patients is unusually vulnerable after vaccination, that distinction might then clue scientists into which cells and molecules are most crucial for protection. “The composite picture can really tell you a lot,” Wherry said. Data like these could help tailor future vaccines to immune systems that have been altered by drugs or disease, or that have simply aged out of maximal protection.

In early results, researchers are already seeing how different groups of immunocompromised people are varying in their response to the shots. Ghady Haidar, a transplant infectious-disease physician at the University of Pittsburgh, told me that his team did not detect antibodies in about 46 percent of blood-cancer patients who had received both doses of the Pfizer or Moderna vaccine. Two studies

out of Johns Hopkins University found no evidence of antibodies in 26 percent of people with rheumatic or musculoskeletal disease (a group that includes rheumatoid arthritis and lupus), and 83 percent of organ-transplant recipients, after their first dose of the Pfizer or Moderna vaccine. Dorry Segev, a transplant surgeon and an author of both studies, told me that his team will soon publish data that show those percentages do drop after the second vaccine dose, down to below 50 percent or so in the transplant group. Still, across studies, even patients who did produce antibodies seemed to mount a somewhat muted response.

For many people in these studies, negative antibody results have been a source of anxiety, especially while vaccinated friends and family are presumably antibody-rich and beginning to venture back into public. Rick Phillips, who is participating in Johns Hopkins's research, told me he was "very stressed" to discover that he had not produced detectable antibodies in response to his first vaccine dose; he'll be taking another test tomorrow to see if the second shot made a difference. But these early antibody data have big caveats. Measuring antibody levels captures only a small subset of the immune system's protective potential, which includes a dizzying array of other cells. In some cases, antibodies might be almost entirely dispensable, as long as there are other immune defenders to fill the void. "The immune system doesn't put all its eggs in one basket," Wherry said.

[Read: Leave your antibodies alone]

Researchers also don't yet know the quantity or quality of antibodies necessary to guard against the coronavirus or the symptoms it can cause. The vaccines available in the United States all tickle typical immune systems into making gobs and gobs of antibodies—very possibly more than is absolutely necessary to guard against the coronavirus. People with ostensibly healthy immune systems exhibit an enormous range of antibody responses to vaccines. So for individuals, low antibody levels shouldn't be cause for panic, Robin Avery, one of the authors on the Johns Hopkins transplant study, told me. Even if antibody levels fall below the as-yet-undefined threshold of complete protection, the molecules might still be abundant and potent enough to curb the severity of symptoms, as they often do when the flu vaccine is given to people who are immunocompromised. (For these reasons and more, nearly every expert I spoke with advised extreme caution against, or actively discouraged, seeking out commercial antibody tests—many of which don't even look for the

antibodies that will be produced after a vaccine—as a way to test whether a shot was "successful.")

If certain people are confirmed to be less protected by current vaccine regimens, they'll likely have other options for protection. Haidar, of the University of Pittsburgh, noted that people who don't produce antibodies in response to the hepatitis B vaccine, for example, will sometimes be administered a second three-dose series of the vaccine. Avery, of Johns Hopkins, also noted that older people, whose immune systems tend to be a little sluggish, are given higher doses of flu vaccines, which might have a better shot at jump-starting their cells. And early trials in nursing homes have hinted that monoclonal-antibody treatments can be administered as a preventive to keep coronavirus infections at bay—a sort of temporary pseudo-vaccine. None of these options has yet been rigorously tested, though. For now, there's a clear approach for immunocompromised people, Dorlan Kimbrough, a neurologist who treats people with multiple sclerosis at Duke University, told me. As one of his colleagues put it: "Get vaccinated, but behave as though you're not."

In some ways, the habits many people adopted during the pandemic are familiar for immunocompromised people. "We don't spend a lot of time out and about in crowds," Toni Grimes, a 48-year-old retired Army major in Phoenix, Arizona, who takes rituximab for lupus, told me. "The way everything felt with the pandemic—masks, hand sanitizing, staying away from people who are sick—we already do that every day." But as vaccinated friends and family loosen up on masking and distancing, some people, like Patty Adair, 74, of Newton, Massachusetts, have felt left behind. Adair takes a heavily immunosuppressive drug called mycophenolate, which subdues both B cells and T cells, to treat her autoimmune hepatitis, and worries that the treatment hampered her ability to respond to the Moderna vaccine, which she completed in early March. "I feel almost as vulnerable as before I had the vaccine," she told me. "I have done so much to keep safe over this past year. I would not change any of it. But I'd just like to feel a little safer."

[Read: Pregnant? The vaccine may protect you and your baby]

For now, immunocompromised people will have to rely on those who *can* confidently derive protection from vaccines, such as household members, health-care providers, and other close contacts. That puts some of the onus on the rest of

the world: “Every vaccine that goes into an arm is protection for these people,” Longbrake, of Yale, said.

The cost of neglecting the health of immunocompromised people can be staggeringly high. It will be far harder to stop the coronavirus from spreading if entire swaths of people remain unprotected. Those who struggle to clear the virus may also end up harboring it for months at a time, allowing it to mutate before it hops to another host. “This is how some variants emerged,” Ali Ellebedy, an immunologist at Washington University in St. Louis, who is studying vaccine responses in immunocompromised patients, told me. It’s a clear reason, he and many others noted, to ensure the needs of these individuals are understood and met, for their sake and everyone else’s.At home in Indianapolis, Rick Phillips remains hunkered down. Sheryl, his wife, is becoming “more adventurous” by the day, Rick told me. It’s painful, he said, to have to keep turning down lunch invitations from old work colleagues and friends, and to still not know when he’ll next see his grandchildren. He is already seeing the world inch forward without him. But Rick plans to stay the course; he can’t risk making any other choice. “We’re too close to the end,” he said. Slip up now, “and you don’t get a second chance.”